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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,660	03/08/2007	Robert Hofmeister	DEBE:066US/10605466	1727

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EXAMINER	
NATARAJAN, MEERA	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
05/05/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

aopatent@fulbright.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,660	HOFMEISTER ET AL.	
	Examiner	Art Unit	
	MEERA NATARAJAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 30-53* is/are pending in the application.

4a) Of the above claim(s) *30-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's amendments in the reply filed on 2/11/2011 is acknowledged and entered into the record.

2. Accordingly, Claims 26, 30-53 are pending. Claims 30-50 have been withdrawn as being drawn to non-elected inventions.

3. Claims 26, 51-53 will be examined on the merits.

New Grounds of Rejection

(Necessitated by claim amendments)

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 26, 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorken et al. (US Patent 7112324) in view of .

7. The claims are drawn to a composition comprising a polypeptide comprising at least two antigen binding sites wherein said at least two antigen binding sites are located on a single polypeptide chain and wherein one antigen binding site specifically binds the human CD3 antigen and the other binding site specifically binds to the human CD19, said polypeptide existing in both monomeric and multimeric form, said multimeric form constitutes no more than 3%, 2% or 1% of the total weight of the combined monomeric and multimeric forms of said polypeptide, and said polypeptide comprises SEQ ID NO:1-6, and said composition further comprises a citrate/lysine buffer pH 6.0-7.5.

8. Dorken et al. teach "single-chain multifunctional polypeptides comprising at least two binding sites specific for the CD19 and CD3 antigen" (see Abstract). Dorken et al. teach a polypeptide with binding sites specifically to human CD19 antigen and wherein said polypeptide has a sequence that is 100% homologous to SEQ ID NO: 1 (see attached alignment). Dorken et al. is silent in regards to the percentage of multimeric form versus monomeric form and does not teach a citrate/lysine buffer with a pH of 6.0-7.5. These deficiencies are made up for by Lee et al. (US Patent 5,917,021) and Kaisheva et al. (PgPub 20030138417).

9. Lee et al. teach methods to increase stabilization and monomeric protein levels in a composition comprising single-chain antigen-binding proteins. Lee et al. teach methods to optimize single-chain antibody compositions to avoid aggregates during

freeze/thaw cycles. Lee et al. teach "biological consistency and stability are essential for most clinical applications of a monomeric, single-chain antigen-binding protein composition". Lee et al. disclose the addition of amino acids such as lysine help stabilize and protect compositions from decomposition. Lee et al .disclose suitable pH ranges for the preparation of the frozen-storage stabilized monomeric protein compositions are about 6 to 8, but more preferably 6.7 to 7.5 and compositions comprising greater than 95% monomers.

10. Kaisheva et al. teach methods of influencing the dimer to monomer transition of an antibody single-chain Fv fragment. Kaisheva et al. disclose lowering the pH and increasing salt can influence monomeric transition. Kaisheva disclose examples of buffers that control the range of pH. Kaisheva et al. disclose citrate as a preferred buffer to keep the pH in the range of 6.0-6.5.

11. It would have been *prima* facie obvious to one of ordinary skill in the art at the time the claimed invention was made to increase the percentage of monomeric forms and increase stability by lowering the pH and adding lysine. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the teachings of Dorken et al., Lee et al. and Kaisheva et al, because Lee et al. teach optimizing single-chain monomeric compositions by adding lysine and lowering pH for clinical applications and Kaisheva et al. teach the use of citrate buffer to maintain a desirable pH in the range of 6.0-6.5 for increased monomerization. It would be obvious to make a composition comprising no more than 1% multimeric form of the

polypeptide taught by Dorken et al. by maintaining a pH in the range of 6-7.5 with increased stability by adding lysine for clinical applications.

Response to Arguments

12. Applicants argue the newly amended claims to include the additional limitations of citrate buffer and lysine further distance the present invention from Dorken. Applicants have filed a declaration by Dr. Thomas Urbig which provides evidence of surprising and unexpected results for the invention as now claimed. These arguments/affidavit have been carefully considered but not found persuasive. As stated in the rejection above, it has been well known in the art that lowering the pH increases monomerization of antibodies. Additionally it has been well established that the addition of amino acids, such as lysine, are used to stabilize antibody compositions. Therefore, the affidavit claiming surprising and unexpected results from a citrate buffer and lysine addition is not found to be persuasive to overcome the rejection.

All previous rejections are withdrawn in view of Applicants amendments to the claims filed on 2/11/2011.

Conclusion

13. Claims 26, 51-53 are rejected.

14. No Claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Friday, 9:00AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MN/

/LAURA B GODDARD/

Primary Examiner, Art Unit 1642